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GUEST EDITORIAL

How Do We Apply Genetic Testing for Breast Cancer Susceptibility to Clinical Practice?

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Sequencing of the *BRCA1* gene in 1994 [1] and the *BRCA2* gene in 1995 [2] means that testing will soon be available that can identify up to 80% of patients in whom hereditary breast cancer will develop. Currently, testing can be carried out only by complex DNA analysis, but in the near future testing will become cheap and simple. As the technical roadblocks are rapidly pushed aside, the social and medical implications of this testing become paramount. Until now, we have been able to hide behind the lack of technology. Many questions are now arising, including: Which patients are likely to carry the genetic mutation? Should they be tested? How should they be informed of the risks and benefit of testing? How do we use the test results? How do we avoid testing the low-risk patient, or should we test everyone?

Even though many breast cancer patients have a family history of the disease, only about 10% of all breast cancers are caused by inherited genetic mutations. The characteristics of hereditary cancer include the presence of breast cancer (and ovarian cancer in *BRCA1* families) in multiple blood relatives and in multiple generations, diagnosis at a young age, and often the presence of bilateral disease. The *BRCA1* gene is responsible for about 45% of hereditary breast cancer, and the *BRCA2* gene for an additional 40%. A female carrier of a mutation in either gene has about a 50% risk of developing breast cancer before the age of 50 and an 87% risk by age 70. The female *BRCA1* carrier also harbors a 40–60% risk of developing ovarian cancer by age 70.

Genetic testing for breast cancer susceptibility has great potential benefit for women in families with hereditary breast cancer, perhaps, most importantly because it carries the possibility of avoiding unnecessary prophylactic surgery. In the past, the best we could say was that a women in such a family had a 50:50 chance of developing cancer. This was often considered sufficiently high to warrant prophylactic mastectomy with its inherent medical and psychological morbidity. In *BRCA1* families, consideration was also given to prophylactic oophorectomy with its even greater long-term health-related consequences (e.g., osteoporosis, heart disease). We will soon be able to test our patient before considering surgery and, with a large degree of accuracy, determine whether she is a gene carrier with a breast cancer risk of 87% or is not a carrier and her risk is equal to that of the general population. Today, no woman should undergo this prophylactic surgery without first being tested for the genetic mutation.

In addition, the test can provide relief from uncertainty, allow planning for the future, and clarify risks for relatives. The patient who learns she is not a carrier will be relieved to find she does not carry the family risk and that her daughters are not at risk. In addition, she can eliminate consideration of prophylactic surgery or chemoprevention and the need for intensive surveillance.

Keeping in mind the great potential benefits, it is now essential to step back and consider that this is not the average clinical test. Ordering this test is not like ordering a test to determine a cholesterol level. Testing requires consideration of issues involving not just the patient in front of you, but also the patient's family. Before your patient can be tested, an affected family member must be identified and tested. The *BRCA1* gene is encoded by 5,593 nucleotides in 22 exons. To date, more than 100 different mutations have been identified. The number of mutations for *BRCA2* is not yet known but may well be of a similar magnitude. Therefore, at our current level of technology, we must identify the mutation specific to that family before testing women at risk in the family.

What is the predictive value of the test? If the affected relative tests negative, it may not completely rule out hereditary cancer, because of several problems including:

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the family member tested may be a sporadic case, the family cancers may result from a gene other than *BRCA1* or *BRCA2*, or the mutation may be in the regulatory part of the gene and not be found by current testing methods that only sequence the exons.

If the family member tests positive, you will have identified the family-specific mutation. If your patient tests negative for that mutation, she can be reassured that she is not at extremely high risk of hereditary cancer, but she remains at the population risk and cannot be ignored.

However, if your patient tests positive, her risk of breast cancer is extremely high, but not 100%, because the gene is not completely penetrant. There appears to be an incompletely understood mutation-specific risk of ovarian cancer as well. Not all *BRCA1* mutations carry the same risk of ovarian cancer, and the breast cancer risk may also vary with the mutation.

Testing is now in the foreseeable future for both genes and clearly offers great potential benefit in selected cases. However, until the benefits and effects of genetic susceptibility are better understood, the Advisory Council for the National Center for Human Genome Research, the National Breast Cancer Coalition, and the American Society of Human Genetics advise that testing be offered only to members of selected high-risk families as part of investigational protocols specifically designed to evaluate the psychosocial and medical impact.

With the potential benefits described, why is such caution advised? In general, it is to protect the patient from all the potential social, psychologic, and medical risks of the test. The greatest concern currently is the risk of insurance discrimination. A woman who tests positive may lose her health insurance coverage or may be subjected to higher premiums. In addition, she may find herself unable to obtain life or disability insurance or may be covered only at a markedly increased cost. Legislative protection from insurance discrimation is currently found in only 11 states and may require federal action to be comprehensive.

Of only slightly less concern is employment discrimination. Even though patients with genetic susceptibility are protected under the Americans with Disabilities Act, subtle discrimination such as being passed over for promotion may go unrecognized or be solved only through litigation.

In terms of psychological adjustment to the test results, your patient will require support regardless of the result as she comes to grips with either an extremely high risk of cancer or the survivor guilt that may accompany a negative result.

Because the underlying principle of any clinical test is to use the information obtained, it is imperative that you have a clear idea of what you will do with a positive result.

The absolute cancer risk remains unclear. Therefore, it will be hard to predict when or if cancer will occur. Most of the information available today is based on extremely high-risk families with a high likelihood of cancer. As more and more patients are tested whose families have a lower rate of cancer, will they have the same 87% lifetime risk? To answer this question, intensive study of affected families, including the collection and interpretation of large numbers of pedigrees, will be required. Even if we assume this markedly increased risk applies to your patient, what should you advise? Prophylactic mastectomy or oophorectomy may appear to be the logical approach, but these operations should not be undertaken lightly. The physical and psychological morbidity, both immediate and long term, must be considered and studied. What is the long-term effect of estrogen deprivation? Can these high-risk patients be placed on estrogen replacement therapy after oophorectomy? What is the appropriate timing of intervention? In addition, the patient must be apprised that these procedures are not 100% effective. Breast cancer can occur after prophylactic mastectomy, and ovarian cancer can occur after prophylactic oophorectomy.

On the other hand, what is the efficacy of screening in this population? Can we be sure that we will identify the cancers in time when they occur? One-half of these patients develop breast cancer before the age of 50, and 20% before the age of 40. Mammography is known to be less effective in these age groups. Screening for ovarian cancer is even less effective. Chemoprevention would be ideal, but no agent has proven efficacy. As gene carriers are identified, it is essential that those who opt for close observation be offered the opportunity to enter chemoprevention trials.

If your patient wishes to be tested, remember that an affected family member must be tested. As health care providers, we are usually only responsible for the patient in front of us, and we are less apt to consider our responsibility to family members who are not our patients. Yet, in this instance, we are asking a family member to be tested to help our patient. The family member must be apprised of all the risks and benefits of testing as well. What if the only affected relative does not want to be tested? How far do you pursue this for the benefit of your patient? Once a patient is identified as a carrier, every member of her family is at risk of being a carrier as well. What is your responsibility to these other family members? If your patient does not want to disclose that she is a carrier, you are bound not to relate this information to her family members who are at greatly increased risk.

The patient who presents to you with questions about genetic testing requires a response that considers the issues addressed here. A woman with a single first-degree relative with breast cancer is not likely to benefit from testing. She may be relieved by assessment of her risk based on the model developed by Claus and associates [3] that estimates risk based on family history and the

ages at diagnosis. For example, if she has one first-degree relative diagnosed after age 50, her risk is similar to that of the average woman.

However, a woman who has several close relatives who were diagnosed at young ages has reason to believe that she is at very high risk. Her questions and concerns may not be easily addressed in the context of a routine office visit. If considering testing, she should be educated about the basics of cancer development, cancer genetics, the current technology of predisposition testing, and the predictive value of the test. Extensive discussions are required to ensure that she makes a fully informed decision about testing. The woman and her family members who choose testing, as well as their health care providers, should be prepared to do so with a strategy in mind to maximize the benefits of testing.

Disclosure of results should be accomplished within the context of a counseling session, during which discussion of the implications of the result and how they relate to the pretest strategy takes place. This is necessary regardless of the results, because even a negative result requires psychological adjustment.

The medical and lay communities are becoming increasingly aware of genetic testing, as progress in molecular genetics is made and publicized. Your patients will be asking you about testing. The vast majority can be reassured that testing is not useful for them. However, for the select group of patients who may be eligible for testing, a comprehensive approach is necessary. This can best take place in a cancer risk counseling program staffed by specially trained nurses or genetic counselors and physicians qualified to interpret family pedigrees, to educate and counsel individuals and families, and to recommend action plans if testing is undertaken. Most of these programs will offer testing under a research protocol designed to identify high-risk individuals and study the effects and implications of testing.

The age of genetic testing for cancer susceptibility has arrived. The issues are no longer technical. Testing will become easier and cheaper to do. The medical community needs to quickly educate itself regarding this technology and the medical, legal, and ethical issues involved and to be prepared to share this knowledge responsibly with patients.

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